

Sub G17 B7
What is claimed is:

1. A method for determining susceptibility for an HCV anti-viral drug comprising:

5 (a) introducing a resistance test vector comprising a patient-derived segment which comprises a hepatitis C virus gene and an indicator gene into a host cell;

(b) culturing the host cell from (a);

(c) measuring expression of the indicator gene in a target host cell; and

(d) comparing the expression of the indicator gene from (c) with the expression of the indicator gene measured when steps (a)-(c) are carried out in the absence of the anti-viral drug,

wherein a test concentration of the HCV anti-viral drug is present at steps (a)-(c); at steps (b)-(c); or at step (c).

20 2. The method of claim 1 wherein the resistance test vector comprises DNA of a genomic viral vector.

3. The method of claim 1 wherein the resistance test vector comprises RNA of a genomic viral vector.

25 4. The method of claim 1 wherein the resistance test vector comprises genes encoding C, E1, E2, NS2, NS3, NS4, or NS5.

30 5. The method of claim 1 wherein the patient-derived segment comprises a functional viral sequence.

6. The method of claim 1 wherein the patient-derived segment encodes one protein that is the target of an anti-viral drug.

7. The method of claim 1 wherein the patient-derived segment encodes two or more proteins that are the target of an anti-viral drug.

5
~~10 11 12 13 14 15~~ 8. The method of claim 5 wherein the functional viral sequence comprises an TRES.

10 9. The method of claim 1 wherein the indicator gene is a functional indicator gene and the host cell is a resistance test vector host cell including the additional step of infecting the target host cell with resistance test vector viral particles using filtered supernatants from said resistance test vector host cells.

15 10. The method of claim 1 wherein the indicator gene is a non-functional indicator gene.

20 11. The method of claim 10 wherein the host cell is a packaging host cell/resistance test vector host cell.

12. The method of claim 11 wherein the culture is by co-cultivation.

25 13. The method of claim 11 wherein the target host cell is infected with resistance test vector viral particles using filtered supernatants from said packaging host cell/resistance test vector host cells.

30 14. The method of claim 1 wherein the indicator gene is a luciferase gene.

35 15. The method of claim 1 wherein the indicator gene is an β -lactamase gene.

16. The method of claim 11 wherein the packaging host cell/resistance test vector host cell is a human cell.

5 17. The method of claim 11 wherein the packaging host cell/resistance test vector host cell is a human liver cell.

10 18. The method of claim 11 wherein the packaging host cell/resistance test vector host cell is a Huh7 cell.

15 19. The method of claim 1 wherein the target host cell is a HepG2 cell.

20. A resistance test vector comprising a patient-derived segment comprising a gene of Flaviviridae and an indicator gene.

20 21. The resistance test vector of claim 20, wherein the patient-derived segment comprises a Flavivirus gene.

22. The resistance test vector of claim 20 wherein the patient-derived segment is one gene.

25 23. The resistance test vector of claim 20 wherein the patient-derived segment is two or more genes.

24. The resistance test vector of claim 20 wherein the patient-derived segment comprises an HCV gene.

30 25. The resistance test vector of claim 20 wherein the patient-derived segment comprises the NS3/4A protease gene.

35 26. The resistance test vector of claim 20 wherein the

patient-derived segment comprises the NS5B RDRP gene.

27. The resistance test vector of claim 20 wherein the patient-derived segment comprises the IRES.

5

28. The resistance test vector of claim 20 wherein the indicator gene is a functional indicator gene.

10

29. The resistance test vector of claim 20 wherein the indicator gene is a non-functional indicator gene.

30. The resistance test vector of claim 20 wherein the indicator gene is a luciferase gene.

15

31. A packaging host cell transfected with a resistance test vector of claim 20.

20

32. The packaging host cell of claim 31 that is a mammalian host cell.

25

33. The packaging host cell of claim 31 that is a human host cell.

34. The packaging host cell of claim 31 that is a human liver cell.

35. The packaging host cell of claim 31 that is HepG2.

30

36. The packaging host cell of claim 31 that is Huh7.

37. A method for determining susceptibility for an HCV anti-viral drug comprising:

(a) introducing a resistance test vector comprising a patient-derived segment which comprises a hepatitis C virus gene and a nonfunctional

35

mb/c4

Arb
C4

5 indicator gene into a host cell;
(b) culturing the host cell from (a);
(c) measuring expression of the indicator gene
in a target host cell; and
5 (d) comparing the expression of the indicator gene
from (c) with the expression of the indicator gene
measured when steps (a)-(c) are carried out in the
absence of the HCV anti-viral drug,
10 wherein a test concentration of the HCV anti-viral drug
is present at steps (a)-(c); at steps (b)-(c); or at
step (c).

Arb
C4

15 38. The method of claim 37 wherein the resistance test
vector comprises DNA of a genomic viral vector.

15 39. The method of claim 37 wherein the resistance test
vector comprises RNA of a genomic viral vector.

Arb
C4

20 40. The method of claim 37 wherein the resistance test
vector comprises genes encoding C, E1, E2, NS2, NS3,
NS4 or NS5.

Arb
C4

25 41. The method of claim 37 wherein the patient-derived
segment encodes one protein.

25 42. The method of claim 37 wherein the patient-derived
segment encodes two or more proteins.

30 43. The method of claim 37 wherein the patient-derived
segment comprises a functional viral sequence.

30 44. The method of claim 37 wherein the indicator gene is a
luciferase gene.

35 45. The method of claim 37 wherein the host cell is a

packaging host cell.

46. The method of claim 37 wherein the packaging host cell
is a human cell.

5

47. The method of claim 37 wherein the packaging host cell
is a human liver cell.

10

48. The method of claim 37 wherein the packaging host cell
is a Huh7 cell.

15

49. The method of claim 37 wherein the packaging host cell
is a HepG2 cell.

20

50. The method of claim 37 wherein the nonfunctional
indicator gene comprises a negative sense sequence.

51. The method of claim 37 wherein the host cell and target
cell are the same cell.

25

52. The method of claim 37 wherein the target cell is a
human cell.

53. The method of claim 37 wherein the target host cell is
infected with resistance test vector viral particles
using filtered supernatants from said packaging host
cell/resistance test vector host cell.

30

54. The method of claim 37 wherein said culture is by
co-cultivation.

35

55. A method for determining HCV anti-viral drug resistance
in a patient comprising:
(a) developing a standard curve of drug susceptibility
for an HCV anti-viral drug;

5 (b) determining HCV anti-viral drug susceptibility in the patient according to the method of claim 1; and

(c) comparing the HCV anti-viral drug susceptibility in step (b) with the standard curve determined in step (a), wherein a decrease in HCV anti-viral susceptibility indicates development of HCV anti-viral drug resistance in the patient.

10 56. A method for determining HCV anti-viral drug resistance in a patient comprising:

15 (a) developing a standard curve of drug susceptibility for a HCV anti-viral drug;

(b) determining HCV anti-viral drug susceptibility in the patient according to the method of claim 37; and

(c) comparing the HCV anti-viral drug susceptibility in step (b) with the standard curve determined in step (a), wherein a decrease in HCV anti-viral susceptibility indicates development of HCV anti-viral drug resistance in the patient.

20 57. A method for determining HCV anti-viral drug resistance in a patient comprising:

25 (a) determining HCV anti-viral drug susceptibility in the patient at a first time according to the method of claim 1, wherein the patient-derived segment is obtained from the patient at about said time;

30 (b) determining HCV anti-viral drug susceptibility of the same patient at a later time; and

(c) comparing the HCV anti-viral drug susceptibilities determined in step (a) and (b), wherein a decrease in anti-viral drug susceptibility at the later time compared to the first time indicates

35

JNS
E3

development or progression of HCV anti-viral drug resistance in the patient.

5 58. A method for determining HCV anti-viral drug resistance in a patient comprising:

*INS
EB*

- (a) determining HCV anti-viral drug susceptibility in the patient at a first time according to the method of claim 37, wherein the patient-derived segment is obtained from the patient at about said time;
- (b) determining HCV anti-viral drug susceptibility of the same patient at a later time; and
- (c) comparing the HCV anti-viral drug susceptibilities determined in steps (a) and (b), wherein a decrease in HCV anti-viral drug susceptibility at the later time compared to the first time indicates development or progression of HCV anti-viral drug resistance in the patient.

20 59. A method for determining susceptibility for an HCMV anti-viral drug comprising:

- (a) introducing a resistance test vector comprising a patient-derived segment which comprises a HCMV gene and an indicator gene into a host cell;
- (b) culturing the host cell from (a);
- (c) measuring expression of the indicator gene in a target host cell; and
- (d) comparing the expression of the indicator gene from (c) with the expression of the indicator gene measured when steps (a)-(c) are carried out in the absence of the anti-viral drug,

30 wherein a test concentration of the HCMV anti-viral drug is present at steps (a)-(c); at steps (b)-(c); or at step (c).

60. The method of claim 59 wherein the resistance test vector comprises DNA of a genomic viral vector.

5 61. The method of claim 59 wherein the resistance test vector comprises DNA of a subgenomic viral vector.

10 62. The method of claim 59 wherein the resistance test vector comprises DNA ~~encoding~~ ^D phosphotransferase (UL97), DNA polymerase (UL54), protease (UL80), UL54, UL44, UL57, UL105, UL102, UL70, UL114, UL98, or UL84.

15 63. The method of claim 59 wherein the patient-derived segment comprises a functional viral sequence.

20 64. The method of claim 59 wherein the patient-derived segment encodes one protein that is the target of an anti-viral drug.

25 65. The method of claim 59 wherein the patient-derived segment encodes two or more proteins that are the target of an anti-viral drug.

30 66. The method of claim 59 wherein the indicator gene is a functional indicator gene and the host cell is a resistance test vector host cell including the additional step of, infecting the target host cell with resistance test vector viral particles.

67. The method of claim 59 wherein the indicator gene is a non-functional indicator gene.

35 68. The method of claim 59 wherein the host cell is a packaging host cell/resistance test vector host cell.

69. The method of claim 68 wherein the culture is by co-cultivation.

5 70. The method of claim 69 wherein the target host cell is infected with resistance test vector viral particles from said packaging host cell/resistance test vector host cells.

10 71. The method of claim 59 wherein the indicator gene is a luciferase gene.

15 72. The method of claim 59 wherein the indicator gene is an β -lactamase gene.

15 73. The method of claim 68 wherein the packaging host cell/resistance test vector host cell is a human cell.

20 74. The method of claim 68 wherein the packaging host cell/resistance test vector host cell is a human foreskin fibroblast cell.

50 75. The method of claim 68 wherein the packaging host cell/resistance test vector host cell is a MRC5 cell.

25 76. The method of claim 59 wherein the target host cell is a human embryonic lung cell.

30 77. A resistance test vector comprising a patient-derived segment which comprises a gene of herpesviridae and an indicator gene.

35 78. The resistance test vector of claim 77, wherein the patient-derived segment comprises a alpha herpesvirinae.

79. The resistance test vector of claim 77 wherein the patient-derived segment is one gene.

5 80. The resistance test vector of claim 77 wherein the patient-derived segment is two or more genes.

81. The resistance test vector of claim 77 wherein the patient-derived segment comprises an HCMV gene.

10 82. The resistance test vector of claim 77 wherein the indicator gene is a functional indicator gene.

15 83. The resistance test vector of claim 77 wherein the indicator gene is a non-functional indicator gene.

15 84. The resistance test vector of claim 77 wherein the indicator gene is a luciferase gene.

20 85. A packaging host cell transfected with a resistance test vector of claim 77.

86. The packaging host cell of claim 85 that is a mammalian host cell.

25 87. The packaging host cell of claim 85 that is a human host cell.

88. The packaging host cell of claim 85 that is a human embryonic lung cell.

30 89. The packaging host cell of claim 85 that is MRC5 cells.

90. The packaging host cell of claim 85 that is a human foreskin fibroblast cell line.

35

5 91. A method for determining susceptibility for an HCMV anti-viral drug comprising:

(a) introducing a resistance test vector comprising a patient-derived segment which comprises a HCMV gene and a nonfunctional indicator gene into a host cell;

10 (b) culturing the host cell from (a);

(c) measuring expression of the indicator gene in a target host cell; and

15 (d) comparing the expression of the indicator gene from (c) with the expression of the indicator gene measured when steps (a)-(c) are carried out in the absence of the HCMV anti-viral drug,
wherein a test concentration of the HCMV anti-viral drug is present at steps (a)-(c); at steps (b)-(c); or at step (c).

20 92. The method of claim 91 wherein the resistance test vector comprises DNA of a genomic viral vector.

25 93. The method of claim 91 wherein the resistance test vector comprises DNA of a subgenomic viral vector.

94. The method of claim 91 wherein the resistance test vector comprises DNA encoding phosphotransferase (UL 97), DNA polymerase (UL54), protease (UL80), UL54, UL44, UL57, UL105, UL102, UL70, UL114, UL98, or UL84.

30 95. The method of claim 91 wherein the patient-derived segment encodes one protein.

96. The method of claim 91 wherein the patient-derived segment encodes two or more proteins.

35 97. The method of claim 91 wherein the indicator gene is a

luciferase gene.

98. The method of claim 91 wherein the host cell is a packaging host cell.

5 99. The method of claim 91 wherein the packaging host cell is a human cell.

100. The method of claim 91 wherein the packaging host cell is a human embryonic lung cell.

10 101. The method of claim 91 wherein the packaging host cell is a human foreskin fibroblast.

15 102. The method of claim 91 wherein the nonfunctional indicator gene comprises a permuted promoter.

103. The method of claim 91 wherein the nonfunctional indicator gene comprises a permuted coding region.

20 104. The method of claim 91 wherein the host cell and target cell are the same cell.

105. The method of claim 91 wherein the target cell is a human cell.

25 106. The method of claim 91 wherein the target host cell is infected with resistance test vector viral particles from said packaging host cell/resistance test vector host cell.

30 107. The method of claim 106 wherein said culture is by co-cultivation.

35 108. A method for determining HCMV anti-viral drug

resistance in a patient comprising:

- (a) developing a standard curve of drug susceptibility for an HCMV anti-viral drug;
- (b) determining HCMV anti-viral drug susceptibility in the patient according to the method of claim 59; and
- (c) comparing the HCMV anti-viral drug susceptibility in step (b) with the standard curve determined in step (a), wherein a decrease in HCMV anti-viral susceptibility indicates development of HCMV anti-viral drug resistance in the patient.

109. A method for determining HCMV anti-viral drug resistance in a patient comprising:

- (a) developing a standard curve of drug susceptibility for an HCMV anti-viral drug;
- (b) determining HCMV anti-viral drug susceptibility in the patient according to the method of claim 91; and
- (c) comparing the HCMV anti-viral drug susceptibility in step (b) with the standard curve determined in step (a), wherein a decrease in HCMV anti-viral susceptibility indicates development of HCMV anti-viral drug resistance in the patient.

110. A method for determining HCMV anti-viral drug resistance in a patient comprising:

- (a) determining HCMV anti-viral drug susceptibility in the patient at a first time according to the method of claim 59, wherein the patient-derived segment is obtained from the patient at about said time;
- (b) determining HCMV anti-viral drug

susceptibility of the same patient at a later time; and

5 (c) comparing the HCMV anti-viral drug susceptibilities determined in step (a) and (b), wherein a decrease in anti-viral drug susceptibility at the later time compared to the first time indicates development or progression of anti-viral drug resistance in the patient.

10

111. A method for determining HCMV anti-viral drug resistance in a patient comprising:

15 (a) determining HCMV anti-viral drug susceptibility in the patient at a first time according to the method of claim 91, wherein the patient-derived segment is obtained from the patient at about said time;

20 (b) determining HCMV anti-viral drug susceptibility of the same patient at a later time; and

25 (c) comparing the HCMV anti-viral drug susceptibilities determined in steps (a) and (b), wherein a decrease in HCMV anti-viral drug susceptibility at the later time compared to the first time indicates development or progression of HCMV anti-viral drug resistance in the patient.

add Gr 7

00000000000000000000000000000000